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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/081,922	02/21/2002	Julianna Lisziewicz	RGT 9771	4590

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11726 LIGHTFALL COURT
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EXAMINER	
WILSON, MICHAEL C	

ART UNIT	PAPER NUMBER
1632	

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07/12/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/081,922	LISZIEWICZ ET AL.	
	Examiner	Art Unit	
	Michael C. Wilson	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 January 2007 and 27 March 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23-26,28,30-33,35 and 37-43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23-26,28,30-33,35 and 37-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2-21-02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

In view of the supplemental appeal brief filed on 3-27-07, PROSECUTION IS HEREBY REOPENED. A new double patenting rejection and a new indefiniteness rejection are set forth below. References have been added to the 102 and 103 rejections to support an inherency argument (Mittal and Kuby) and do not alter the basis of the rejections.

To avoid abandonment of the application, appellant must exercise one of the following two options:

(1) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or,

(2) initiate a new appeal by filing a notice of appeal under 37 CFR 41.31 followed by an appeal brief under 37 CFR 41.37. The previously paid notice of appeal fee and appeal brief fee can be applied to the new appeal. If, however, the appeal fees set forth in 37 CFR 41.20 have been increased since they were previously paid, then appellant must pay the difference between the increased fees and the amount previously paid.

A Supervisory Patent Examiner (SPE) has approved of reopening prosecution by signing below:

PETER PARAS, JR.
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

For future reference, a corrected Appeal Brief should include a copy of the entire corrected Appeal Brief.

Claims 23-26, 28, 30-33, 35 and 37-43 are pending and under consideration.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Applicant's arguments filed 1-5-07 and 3-27-07 have been fully considered but they are not persuasive.

The Declaration by Dr. Lisziewicz filed 1-5-07 has been fully considered but is not persuasive. Applicants argue the Declaration by Lisziewicz filed 1-5-07 was made of record in this case on Feb 21, 2002. Applicants' argument is not persuasive. The Declaration was first filed in application 10/081922 on 1-05-07 with the Appeal Brief.

Updated initialed copies of the Information Disclosure Statements filed 2-21-02 are provided herewith.

Claim Rejections - 35 USC § 112

Written Description

The rejection of claims 37-39 under written description regarding how to apply a gene delivery complex encoding an HIV protein to the skin or mucosa of an animal such that a therapeutic or prophylactic immune response against HIV is obtained has been withdrawn.

I. Claims 23-26, 28, 30-33, 35 and 37-43 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention for reasons of record.

The number of sugars (sucrose, fructose, glucose, galactose, maltose) and the number of PEI derivatives (sucrosylated, glycosylated, mannosylated, as well as any other derivative of PEI) encompassed by the terms alone are numerous. Therefore, the combination of "one or more" encompasses innumerable combinations of sugars, PEI and PEI derivatives. Claim 23 of the preliminary amendment filed 2-21-02 contemplates using "sugars, polyethylenimine, and polyethylenimine derivatives, and mixtures thereof"; however, this is the only place in the specification that describes "one or more compounds" as now claimed. Pg 15, lines 6-8, contemplates using PEI, specifically modified PEI, more specifically sugar modified PEI, to target the mannose receptor. Pg 15, lines 6-8, does not teach or suggest using one or more sugar, PEI or PEI derivative as claimed. Pg 15, lines 16-17, teach the mannose receptor size and does not teach or suggest using Example 10 and Table 2 teaches:

"Experimental results depicted in Table 2 provided evidence that a sugar-DNA complex, in the absence of PEI-man, can transduce Langerhans cells in vivo. Sugar complexed DNA in the absence of PEI is more efficient for use in both subcutaneous and transcutaneous methods than DNA complexed with PEI (see Table 2, experiments 3 & 5). This is a very surprising result. It shows that sugars (e.g. 8% glucose in these experiments) can also complex DNA and deliver the DNA to the Langerhans cells via the mannose receptor. Importantly, the most efficient gene delivery in vivo to the Langerhans cells was the sugar complexed DNA used in the transcutaneous way." (pg 24).

Thus, Example 10 describes a sugar-DNA complex in the absence of PEI or PEI-derivates. Table 2 (pg 23) discloses using PEI or mannosylated PEI but does not teach combining PEI or mannyosylated PEI in combination with a sugar solution. Example 10 and Table 2 do not teach or suggest using one or more sugar, PEI or PEI derivative as

claimed. Thus, the specification does not provide written description for any specific combination of sugar, PEI and PEI derivatives.

An adequate written description of a combination of elements requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the combinations themselves. It is not sufficient to state a composition comprises one or more sugar, PEI or PEI derivative able to transfect APCs in vivo because disclosure of no more than that, as in the instant case, is simply a wish to know the identity of any combination having that biological property. Also, naming a type of material generically known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. Thus, claiming a method that requires using any combination of sugar, PEI and PEI derivatives that achieve a result without defining what means will do is not in compliance with the description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)).

Response to arguments

The limitation of "one or more compounds selected from the group consisting of sugars, polyethylenimine, and polyethylenimine derivatives" in claim 23 lacks written description. Applicants point to pg 21, Experiment 6, which teaches PEI modified with mannose, galactose and glucose, and pg 22, Experiment 8, which teaches PEI modified with mannose combined with glucose solution. Applicants submit these citations are sufficient to support the phrase in question. Applicants' argument is not persuasive.

Experiment 6 is limited to using one PEI derivative at a time and does not require using more than one compound as encompassed by the phrase "one or more compounds". Experiment 8 is limited to mannosylated-PEI and glucose solution. The number of combinations of sugars (sucrose, fructose, glucose, galactose, maltose), PEI and PEI derivatives (sucrosylated, glycosylated, mannosylated, etc.) encompassed by the phrase in question are significantly greater in scope than mannosylated PEI and glucose as disclosed. The singular combination disclosed in Experiment 8 does not suggest or imply the greater scope claimed. Original claim 23 contemplated sugars, PEI and PEI derivatives and mixtures thereof which also fails to suggest or imply any specific species in the genus. The singular combination disclosed in Experiment 8 in combination with broad genus in original claim 23 ("sugars, PEI, PEI derivatives and mixtures thereof") fails to be adequate written description for the innumerable species encompassed by the phrase "one or more compounds selected from the group consisting of sugars, polyethylenimine, and polyethylenimine derivatives" in claim 23.

Enablement

II. Claims 37-39 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for reasons of record.

Breadth of the claims

Claims 37-39 require applying a gene delivery complex that targets APCs to the skin or mucosa of an animal, wherein the complex comprises i) DNA encoding an

immunogenic protein operably linked to a promoter; and one or more compounds selected from the group consisting of sugars, polyethylenimine (PEI), and PEI derivatives, wherein the protein is from HIV (37), a replication-defective HIV (38), or an integration-defective, replication-defective HIV (39).

The specification describes using the method claimed to induce an immune response in a mammal (pg 20, Example 4). However, merely inducing an immune response in a mammal, in and of itself, does not have an enabled use because inducing an immune response is only described in the specification as being used to obtain a therapeutic or prophylactic effect (pg 2, lines 20-24; pg 18, lines 2-8). Therefore, inducing an immune response against HIV according to the specification must result in a therapeutic or prophylactic effect to have an enabled use. The ordinary artisan reading claims 37-39 in view of the specification would determine that the immune response against HIV protein must be therapeutic or prophylactic. The enablement rejection b) is based on the sole disclosed use for the methods of claims 37-39 – inducing an immune response against HIV that is therapeutic or prophylactic.

State of the art and unpredictability of inducing an immune response capable of treating retroviral infection

The state of the art regarding treating retroviral infection was unpredictable. Stricker of record (Medical Hypotheses, June 1997, Vol. 48, pages 527-9) teaches that attempts to develop a vaccine against HIV have been unsuccessful because HIV vaccines do not neutralize HIV (pg 527, last paragraph through all of pg 528). Overall, a lack of understanding about protective immunity to HIV in humans, the sequence

variability of HIV and the rapid replication of HIV contribute the ineffectiveness of vaccines against HIV (Bangham of record, Nov. 29, 1997, Lancet, Vol. 350, pages 1617-1621; page 1617, top of col. 1).

More specifically, Veljkovic (Vaccine, 2001, Vol. 19, pg 1855-1862) taught:

> "As was recently reported, the rgp120 subunit vaccine tested in HIV-negative individuals was not only not effective — participants in Phase I:II clinical vaccine trials who have become infected during or following immunization with the HIV-1 env had in their sera significant neutralizing antibody titers against vaccine isolates before they became infected [2,3] — but could also be dangerous [4]." (pg 1856, col. 1, first sentence of the second full paragraph)

Thus, the immune response against an HIV gp120 vaccine is inadequate to provide a prophylactic or therapeutic effect against HIV infection.

In fact, Veljkovic taught HIV could escape recognition by HIV-specific CTL because the virus undergoes mutation within weeks after infection (pg 1857, col. 1, last sentence of the first full paragraph). McMichael explicitly described this phenomenon (Annual Rev. Immunol., 1997, Vol. 15, pg 27-296; see entire article).

Hanke (Immunology Letters, 1999, Vol. 66, pg 177-181) taught administering DNA encoding HIV proteins intradermally caused a CTL response (pg 178, section 2.1). Hanke did not teach the CTL response was therapeutic or prophylactic. Hanke asks the question whether inducing a CTL response can protect against HIV infection and states "CTL per se cannot prevent incoming cell-free virus from infecting host T-cells. However, if there are high levels of memory CTL present in the relevant tissue or circulation and the virus 'challenge" is low, CTL might clear the small number of infected cells before the virus spreads further and establishes generalized infection" (pg 180, col. 1, Section 4.2).

Weber (Eur. J. Clin. Microbiol. Infect. Dis., Nov. 2001, Vol. 20, pg 800-803) described the phase I clinical trial using plasmid encoding HIV-1 gp160 to treat HIV-infected humans. "Even though both trials were designed as phase I clinical trials, with special focus on safety, preliminary data suggest that vaccination with the present HIV-1 DNA construct did not show any virological or immunological efficacy, which is in contrast to findings in the chimpanzee model" (pg 802, col. 2, first sentence of first full paragraph). Thus, plasmid DNA encoding gp160 does not have a therapeutic effect in humans and using DNA encoding HIV proteins in primate models does not correlate to expected results in humans.

Ready (Nature Medicine, (April 2003, Vol. 9, No. 4, pg 376) clearly states that HIV vaccines capable of preventing infections in humans was not predictable (col. 1, last full ¶) and that the road to such a vaccine "is littered with abandoned candidates" (col. 1, last 4 lines). For example, a canarypox vaccine failed to induce a powerful enough immune response (sentence bridging columns 1 and 2). In another trial, three or four monkeys treated with a promising DNA vaccine have died due to viral breakthrough (column 2, first full sentence).

Lori (Current Medical and Chemical Anti-Infective Agents, 2004, Vol. 3, pg 31-41) taught that inducing an HIV-specific immune response in vivo against HIV protein fails to provide a therapeutic or prophylactic effect (pg 31, col. 1, 2nd ¶, lines 7-10).

Dong (J. Exp. Med., Dec. 20, 2004, Vol. 200, No. 12, pg 1547-1557) taught, "HIV-specific cytotoxic T lymphocytes (CTL) are important in controlling HIV replication, but the magnitude of the CTL response does not predict clinical outcome" (first

sentence of abstract, emphasis added). The CTL response generated against HIV-1 proteins has no correlation with either the magnitude/breadth of the response or the plasma viral load (pg 1547, col. 2, first full sentence). In other words, obtaining a CTL response against HIV proteins does not predict the clinical response.

Teachings in the specification

Applicants taught using the LW/int- plasmid encoding replication-defective, integrase-defective retroviral DNA in the claimed invention ((pg 13, lines26-37), described in related application 08/803,484).

Example 4 teaches transfecting dendritic cells in vitro with the LW/Int- plasmid and injecting the dendritic cells into monkeys (split subcutaneously and intravenously). One monkey showed a CTL response (pg 20, lines 8-19).

Example 9 teaches applying a gene delivery complex encoding GFP to the skin of mice. GFP was expressed in dendritic cells.

The specification teaches making plasmids encoding replication defective, integrase-defective HIV as described in application 08/989,301 (pg 18, line 30-32). In application 08/939,301, applicants call such retroviruses "Class 4" viruses that are infectious but replication-defective (pg 15, lines 1-5). In application '301, applicants teach that a replication defective HIV that fails to replicate effectively is inadequate to elicit a protective cellular immune response. On the other hand, a replication defective HIV will still cause HIV (pg 3, line 17 through pg 4, line 3). Therefore, applicants' idea was to find an HIV vector that had enough infectivity/replication to induce a therapeutic immune response against HIV without causing HIV syndrome. '301 taught numerous

HIV vectors that had decreased replication and some that induced an immune response against HIV, but '301 did not teach any HIV vectors that induced a therapeutic or prophylactic immune response against HIV or any HIV vectors that had enough infectivity/replication to induce a therapeutic immune response against HIV without causing HIV syndrome.

Rejection

Claims 37-39 are not enabled because the specification does not provide adequate guidance for one of skill to use the method for its sole disclosed use – to induce a therapeutic or prophylactic immune response by applying a gene delivery complex encoding HIV to the skin or mucosa of an animal.

Example 4 does not correlate to the claimed invention because dendritic cells were transfected in vitro and because the gene delivery complex was not applied to the skin or mucosa as claimed. Furthermore, merely inducing a CTL in one monkey by administering transfected dendritic cells as described in Example 4 is not statistically significant; the observed CTL response may have been a random event and not caused by the administration of dendritic cells. Finally, inducing a CTL response against HIV in vivo as described in Example 4 is not adequate to treat or prevent HIV infection. According to Weber (cited above), DNA encoding HIV proteins may induce an immune response without treating or preventing HIV. Nowhere have applicants provided any evidence that the CTL response observed is adequate to treat or prevent HIV or that the virus does not replicate too much and cause disease. As such, use of DNA encoding HIV proteins as described in Example 4 would not treat or prevent disease because the

virus would replicate and cause disease and because the CTL response observed is inadequate to overcome HIV infection.

Example 9, pg 23-24, does not correlate to the claimed invention because it does not disclose delivering DNA encoding HIV proteins to the skin, inducing an immune response against the protein encoded by the DNA (GFP), or inducing a therapeutic or prophylactic immune response against HIV proteins.

'301 taught numerous HIV vectors that had decreased replication and some that induced an immune response against HIV, but '301 did not teach any HIV vectors that induced a therapeutic or prophylactic immune response against HIV or any HIV vectors that had enough infectivity/replication to induce a therapeutic immune response against HIV without causing HIV syndrome. Thus, it was unknown how to use an HIV vector to obtain a therapeutic or prophylactic immune response against HIV in a host.

The specification does not provide adequate guidance regarding how to obtain a therapeutic or prophylactic effect by applying DNA encoding a replication defective retrovirus in an animal. The specification does not teach the amount of a cellular immune response that is therapeutic or prophylactic effect against a replication defective retrovirus. The amount of dendritic cells required to obtain adequate antigen presentation is not provided in the specification. The amount of retroviral protein expression required to obtain the desired cellular immune response is not provided in the specification. The amount of replication and infectiousness required to obtain the desired balance between therapy and pathogenicity is not provided in the specification. Given the teachings in the specification taken with the unpredictability in the art at the

time of filing, it would have required one of skill in the art at the time of filing undue experimentation to determine how to make and/or use a replication defective retrovirus to obtain a therapeutic/prophylactic effect without causing disease or death.

In addition, it was unpredictable what vector, promoter, dosage, cells, level of expression and route of administration would provide a therapeutic or prophylactic effect using *in vivo* or *ex vivo* gene therapy (Miller 1995, FASEB J., Vol. 9, pg 190-199; pg 198, col. 1; Deonarain, 1998, Expert Opin. Ther. Pat., Vol. 8, pg 53-69; pg 53, 1st ¶, pg 65, 1st ¶ under Conclusion section; Verma, Sept. 1997, Nature, Vol. 389, pg 239-242; see entire article, specifically pg 240, sentence bridging col. 2 and 3; Crystal, 1995, Science, Vol. 270, pg 404-410, pg 409; Ross, Sept. 1996, Human Gene Therapy, Vol. 7, pg 1781-1790; pg 1782, col. 2, 1st full ¶; pg 1789, col. 1, 1st ¶, all of record).

The specification does not enable applying DNA encoding a lentiviral protein to the skin or mucosa to transfect APCs and obtain a therapeutic or prophylactic effect. The specification does not teach applying DNA to the mucosa results transfection of APCs or in expression of the protein in the APCs. The specification does not teach the amount of lentiviral protein expression required for the APCs to present adequate antigens to the immune system such that a therapeutic/prophylactic immune response is obtained. The specification does not teach the immune response to a lentiviral antigen required to treat or prevent disease. The specification does not provide the combination of vector, promoter, dosage, level of expression that would result in a therapeutic/prophylactic effect. Given the teachings in the specification taken with the unpredictability in the art at the time of filing, it would have required one of skill in the art

at the time of filing undue experimentation to determine the vector, promoter, cell, dosage, level of expression and route of administration required to obtain a therapeutic or prophylactic effect using the method claimed.

Response to arguments

Applicants' discussion of en re Brana is noted but is misplaced because it relates to utility and not enablement.

Applicants' discussion of the Wands factors is noted; however, the Examiner's analysis discusses all of the Wands factors. Applicants' discussion does not set forth any error in the examiner's Wands factor analysis.

Applicants' discussion of pertinent law to the claimed invention is noted; however, the examiner has based the enablement rejection on the claims read in light of the specification, applicable law including case law and scientific reasoning.

Applicants argue the claimed invention is "acknowledged to be enabled." Applicants' argument is not persuasive. The claimed invention is not enabled for its sole disclosed use - applying a gene delivery complex encoding an immunogenic HIV protein to the skin or mucosa of a mammal to induce a therapeutic or prophylactic immune response.

Applicants argue whether or not the immune response obtained is a matter for clinical trials and not a matter of enablement. Applicants' argument is not persuasive. Inducing an immune response that is neither therapeutic nor prophylactic using the claimed method does not have an enabled (or disclosed) use.

Applicants argue whether a therapeutic or prophylactic effect is obtained is a matter for the FDA, not the USPTO. Applicants' argument is not persuasive. The claims must have at least one enabled use. In this case, the claims are not enabled for their sole disclosed use.

Applicants argue the "raw materials in question" were used in experiments to induce an immune response ex vivo in Example 4 on pg 20. Applicants argue direct application of a gene delivery complex was shown in Example 9. Therefore, applicants' conclude, "use of the raw material is enabled." Applicants' argument is not persuasive. Neither Example 4 nor 9 resulted in a therapeutic or prophylactic immune response. More specifically, Example 4 teaches obtaining a CTL response against HIV; however, the art at the time of filing and since the time of filing provides adequate evidence that the CTL response is inadequate to be therapeutic or prophylactic against HIV. In addition, a CTL response obtained in vitro was known in the art as not being predictive of the CTL response in vivo (Dong cited in the basis of the rejection). Accordingly, Example 4 does not provide reasonable evidence that the CTL response correlates to a therapeutic outcome. In addition, Example 4 is limited to DNA applied to the dendritic cells in vitro and subcutaneous injection of the dendritic cells into a mammal; Example 4 does not correlate to transfecting dendritic cells by applying DNA to the skin or mucosa of a mammal as claimed. Overall, Example 4 does not require applying DNA to the skin or mucosa of a mammal as claimed and does not provide reasonable evidence that the CTL response correlates to a therapeutic outcome.

Example 9 does not describe applying DNA encoding immunogenic HIV proteins to the skin or mucosa or inducing an immune response, specifically an immune response that is therapeutic or prophylactic. Thus, Example 9 does not provide correlate to the claims and does not adequately describe how to use the method claimed for its sole intended use – to induce an immune response capable of treating or preventing HIV.

Examples 4 and 9 or their combination do not provide adequate guidance that applying DNA encoding an immunogenic HIV protein to the skin or mucosa of a mammal would induce a therapeutic or prophylactic immune response.

Applicants argue the Declaration by Lisziewicz filed 1-5-07 was made of record in this case on Feb 21, 2002. Applicants' argument is not persuasive. The Declaration was first filed 1-05-07 with the Appeal Brief. Applicants' argue the Declaration by Dr. Lisziewicz filed 1-5-07 overcomes the enablement rejection because it shows a therapeutic result. The declaration teaches treating macaques with "a novel immune therapy, called DermaVir." Paragraph 4 on pg 6 of the declaration states: "DermaVir is a product name for an embodiment of the present invention, a complex of PEI-mannose and plasmid DNA encoding an integrase-defective SHIV (Simian-Human Immunodeficiency Virus) in sugar-water solution." It is noted that the Declaration does not teach the sugar used in the "sugar-water." The Declaration states: "The animals continued a fixed-scheduled STI-HAART protocol, and DermaVir treatment was initiated in combination with HAART during the treatment periods." The Declaration fails to overcome the enablement rejection because 1) the gene delivery complex used in the

Declaration, DermaVir, is DNA, PEI-mannose and "sugar-water," which has a much narrower scope than the broader gene delivery complex used in the claims; 2) the method in the Declaration required STI-HAART drug therapy in combination with the gene delivery complex, which is greater in reach than the teachings in the specification originally filed; 3) the Declaration does not teach how DermaVir was administered; therefore, the Declaration does not correlate to "applying a gene delivery complex to the skin or mucosa" as claimed; 4) the Declaration does not provide a reasonable indication that the CD8 response obtained (paragraphs 11 and 12) is caused by the gene delivery complex because it does not use scientific controls; and 5) the Declaration does not provide any indication that the CD8 response obtained (paragraphs 11 and 12) is therapeutic.

Applicants argue publications by the inventors confirm the statement on pg 4, lines 7-11, that expression of antigens in APCs may be used to generate efficient CTL response in vivo and has the potential to generate effective vaccine and therapeutic approaches. The references do not overcome the enablement rejection because the references are limited to specific combinations of DNA, delivery vehicles and methods of delivery encompassed by the claims and because the references use method steps (antiviral drug therapy) not disclosed in the original specification.

Applicants argue Lisziewicz (J. Invest. Derm.) details the use of the present invention to produce a CTL response. It is noted that Lisziewicz (2004) provided by applicants appears to be a copy of the article from the publisher. The correct citation for the article is J. Invest. Derm., Jan. 2005, Vol. 124, No. 1, pg 160-169, hereby referred to

as Lisziewicz (2005). Please use the correct citation especially when citing the reference in front of the board.

Applicants argument is not persuasive because the specific combination of DNA, PEI-mannose and glucose described by Lisziewicz (2005) does not have support in the specification as originally filed, because the narrow limitation of applying DNA, PEI-mannose and glucose topically as described by Lisziewicz (2005) does not enable the combination of elements as broadly written and because Lisziewicz (2005) did not teach the CTL response was therapeutic or prophylactic.

Lisziewicz (2005) taught using DermaVir to make particles containing DNA, PEIm and glucose and administering the complex on about 40 cm2 skin at four locations: the left and right upper inguinal region and left and right axillary region for 30 minutes (pg 167, col. 1, "Topical and *ex vivo* DermaVir immunization"). The structure of DermaVir is described as being "formulated to make a approximately 100 nm particle containing DNA, PEIm, and glucose" (pg 167, col. 1, "Topical and *ex vivo* DermaVir Immunization" of Lisziewicz (2005)). The specific structure of DermaVir is not described. Furthermore, the combination of DNA, PEIm and glucose described by Lisziewicz (2005) does not have support in the instant specification. While the preliminary amendment contemplates using sugars, PEI, PEI derivatives or mixtures thereof (claim 23), the specification as originally filed does not contemplate the specific combination of DNA, PEI-mannose and glucose. Given the innumerable combinations of sugars, PEI and PEI derivatives, the specification as originally filed does not reasonably lead those of skill to the conclusion that applicants contemplated the specific combination of DNA,

PEI-mannose and glucose as described by Lisziewicz (2005). Accordingly, the teachings of Lisziewicz (2005) cannot be relied upon for enablement.

Furthermore, Lisziewicz (2005) is limited to gene delivery particles containing plasmid DNA, PEI-mannose and glucose applied topically (pg 166, col. 2, 1st full ¶), which cannot be relied upon for enablement of the gene delivery complex described in the instant application or to applying the complex to the skin or mucosa as now claimed.

Finally, Lisziewicz (2005) induced CD4 helper and CD8 cells but did not obtain a therapeutic or prophylactic effect against HIV. However, Ready (Nature Medicine, (April 2003, Vol. 9, No. 4, pg 376) clearly states that HIV vaccines capable of preventing infections in humans was not predictable (col. 1, last full ¶) and that the road to such a vaccine "is littered with abandoned candidates" (col. 1, last 4 lines). Furthermore, obtaining a CTL response against HIV as taught in Lisziewicz (2005) is not predictive of the clinical outcome (Dong cited above). Finally, Lori (Current Medical and Chemical Anti-Infective Agents, 2004, Vol. 3, pg 31-41), one of the inventors in the instant application, taught that inducing HIV-specific antibodies failed to provide a protective effect (pg 31, col. 1, 2nd ¶, lines 7-10). Lori also says inducing a cellular immune response will not prevent HIV infection (pg 31, col. 2, first sentence of the new paragraph). While Lori suggests a cellular immune response may treat HIV in the same sentence, Lori does not teach the CTL response required to do so. Applicants have not provided any evidence or any reasonable expectation that CD4 and CD8 cells that recognize HIV proteins overcomes such unpredictability so that a therapeutic or prophylactic effect would be obtained. Without such guidance, merely inducing CD4

helper and CD8 cells that recognize HIV proteins as described by Lisziewicz (2005) is not adequate to enable inducing an immune response against HIV proteins that is therapeutic or prophylactic.

As such, Lisziewicz (2005) cannot be relied upon for enablement of the instant application because it required combining DNA, PEIm and glucose, which does not have support in the instant application, because neither the instant application or Lisziewicz (2005) disclose the structure of DermaVir and because inducing a CD4 and CD8 response against HIV does not induce a therapeutic or prophylactic effect against HIV.

Applicants discuss Lisziewicz (AIDS, 2005, Vol. 19, pg 35-43; referred to as Lisziewicz (2005b). Lisziewicz (2005b) is not persuasive because it is limited to the pLW/int vector, which was not disclosed in the specification as originally filed. Lisziewicz (2005b) is limited to treating with $DermaVir_{SHIV}$ in combination with HAART antiretroviral therapy; however, the combination is greater in reach than the method contemplated in the specification as originally filed. It is also noted that Lisziewicz (2005b) is limited to using PEI for transfection; however, claim 23 is not. Lisziewicz (2005b) is limited to using a plasmid encoding an integrase defective retrovirus for transfection; however, claim 23 is not.

Applicants argue Lisziewicz (2001) taught using plasmid LW/int- and refers to US application 08/803484 in Example 1 (pg 18, line 31) of the instant application. Therefore, applicants' conclude Lisziewicz (2001) correlates to the claimed invention. Applicants' argument is not persuasive. The instant application does not teach the

structure of the LW/int- plasmid. While application '484 taught numerous vectors, '484 did not mention the LW/int- vector or describe any vector having six stop codons, one deletion in the pol region, one stop codon and one deletion in the second reading frame that is integrase negative as described in Lisziewicz (2001). Therefore, the reference on pg 18, line 31, to application 08/803484 is not enabling for those of skill to make the LW/int- vector. Furthermore, Lisziewicz (2001) did not obtain a CTL response capable of treating or preventing HIV. It was known that inducing an HIV-specific immune response in vivo against HIV protein failed to provide a therapeutic or prophylactic effect (Lori and Ready, of record). Applicants have not provided any evidence or any reasonable explanation that the CTL response against HIV obtained in Lisziewicz (2001) overcomes such unpredictability so that a therapeutic or prophylactic effect would be obtained.

Applicants argue where experimental results are shown, the state of the art is irrelevant. Applicants' argument is not persuasive. The experiments in the specification do not provide adequate guidance to overcome the art-established unpredictability of gene therapy or that inducing a CTL or antibody response against HIV antigen in vivo will be therapeutic or prophylactic. The Lisziewicz references (2001, 2005, 2005b) do correlate to the breadth now claimed for reasons of record and provide method steps not originally disclosed.

Applicants argue the invention does not use a retrovirus with a finely tuned reproductive capacity. Applicants' argument is unclear. It is noted the specification clearly suggests finding a DNA encoding a replication-defective integrase-defective

retrovirus that is has adequate replication that would provide an adequate cellular immune response without causing disease. However, applicants do not disclose any such DNA. Applicants have not provided adequate guidance that DNA encoding HIV antigens as claimed are capable of inducing a therapeutic or prophylactic immune response without causing disease.

Applicants argue DermaVir mentioned in Lisziewicz (2005b) is pLW/int- disclosed in Lisziewicz (2001). The instant application and parent application 08/803484 do not teach the structure of the LW/int- plasmid. See discussion of Lisziewicz (2001).

Applicants argue the failure of the vaccine trial in Lori (2004) merely confirms the inventors own disclosure of the need for other materials. Applicants' argument is not persuasive because it essentially indicates the embodiments claimed disclosed by Lori (2004) that relate to the claims are not enabled and others should be sought. Applicants argue the method of Lori (2004) demonstrates failure of others and the results were predicted in application 08/803404 on pg 3, where vaccines directed to the production of an antibody response were disclosed to be problematic for HIV. Applicants' arguments are not persuasive. Lori (one of the inventors in the instant application) also says inducing a cellular immune response will not prevent HIV infection (pg 31, col. 2, first sentence of the new paragraph). While Lori suggests a cellular immune response may treat HIV in the same sentence, Lori does not teach the CTL response required to treat or prevent HIV. The instant application contemplates inducing a cellular immune response; however, claim 23 is not limited to inducing a cellular immune response against HIV, and the instant application does not provide

adequate guidance to use the claimed method to induce a cellular immune response that is therapeutic or prophylactic.

Indefiniteness

The rejection of claims 23-26, 28, 30-33, 35 and 37-43 under 35 U.S.C. 112, second paragraph, regarding the metes and bounds of "transfecting" in claim 23 has been withdrawn in view of pg 6, lines 1-2, which states "the process of modification of cells so that they contain foreign genetic material is called gene transfer, transfection or transduction." Accordingly, "transfection" in claim 23 encompasses any means of modifying cells to contain foreign genetic material.

III. A. Claims 23-26, 28, 30-33, 35 and 37-43 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention because the body of claim 23 merely requires selecting a gene delivery complex that targets APCs and applying a complex to the skin or mucosa surface of an animal, while the preamble requires transfecting of APCs. The body of the claim never requires transfecting APCs or expressing the immunogenic protein in APCs. The preamble and the body of the claim do not have a nexus, thereby making the claim as a whole unclear. The should claim requires a clear positive step in the body of the claim indicating APCs are transfected to be commensurate in scope with the preamble of the claim. Otherwise, those of skill would not be able to determine whether transfecting APCs was an intended use (optional) or whether transfecting must occur.

Applicants' indicate their willingness to amend the claim to resolve the issue but do not argue the rejection.

B. Claims 23-26, 28, 30-33, 35 and 37-43 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention because the metes and bounds of what applicants consider "applying" to the skin in claim 23 cannot be determined. It is unclear if the phrase is limited to putting the complex on the skin or if the phrase encompasses subcutaneous injection which results in delivery of the complex under the skin. It is unclear if intravenous injection is encompassed by the phrase because such an injection does require contact of the complex to the skin when the injection passes through the skin. Pg 16, line 34, states, "The complex can be applied to the skin or mucosa surfaces directly." The citation does not discuss injection or distinguish "applying" from "injecting." As such, one of skill would not be able to determine when they were infringing on the claim. The ordinary definition of applying can mean to put to use or to bring into physical contact with or close proximity to (see definition of applying by Dictionary.com). Intradermal and subcutaneous administration brings the gene complex in physical contact with the skin. Accordingly, applying to the skin or mucosa as claimed encompasses intradermal, subcutaneous or topical administration. The phrase is not limited to topical administration.

Applicants argue the ordinary definition of "applying" was cited. Applicants state the "two are distinct at least as far back as June 7, 2004." Applicants' arguments are

not persuasive. Applicants' definition of "applying" cannot be found, and it is unclear what "two are distinct." Applicants do not argue what breadth is intended by the phrase.

C. Claims 23-26, 28, 30-33, 35 and 37-43 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention because the phrase "gene delivery complex that targets antigen presenting cells" in claim 23 is unclear. It is unclear if the phrase encompasses any gene delivery complex that transfects APCs or if the gene delivery complex has a particular structure or preference for APCs. If the gene delivery complex has a particular structure or preference for APCs, the metes and bounds of those gene delivery complexes that have a preference for transfecting APCs cannot be envisioned. Pg 12, lines 25-27, states: "If the gene delivery complex is made with IgG or a polyethylenimine modified with an appropriate starch or sugar, it will be taken up mainly by antigen presenting cells." Applicants' argument is not persuasive. The phrase claimed does not directly correlate to a gene delivery complex made with IgG or a polyethylenimine modified with an appropriate starch or sugar. The citation does not define the structures within the metes and bounds of the phrase. Nor does the specification define when an antigen presenting cell is targeted or provide an assay for when antigen presenting cells had been targeted. It is not clear whether any sugar can be used to modify PEI to target antigen presenting cells or whether limited types of sugar-modified PEI target antigen presenting cells. Accordingly, those of skill would not be able to determine when they were infringing on the claim.

Applicants argue the phrase is supported by pg 12, lines 25-27, which states: "If the gene delivery complex is made with IgG or a polyethylenimine modified with an appropriate starch or sugar, it will be taken up mainly by antigen presenting cells." Applicants' argument is not persuasive. Applicants' arguments do not address how the citation defines the breadth of the phrase.

D. Claim 30 remains rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention because the phrase "method of claim 28, wherein the complex comprises a 5:1 ratio of polyethylenimine derivative nitrogen per DNA phosphate" remains unclear. Claim 30 does not limit the complex to having polyethylenimine or polyethylenimine derivative; therefore, limiting the complex to having a 5:1 ratio of PEI nitrogen per DNA/phosphate without first limiting the complex to one having PEI does not make sense because the complex can made with sugar (see claim 23). Furthermore, claim 30 refers to a 5:1 ratio of polyethylenimine derivative. It is unclear if applicants are attempting to limit the ratio or the compound used for gene delivery. Overall, the phrase is unclear.

Applicants' indicate their willingness to amend the claim to resolve the issue but do not argue the rejection.

E. Claim 31 remains rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention because it is unclear whether the phrase "is formulated in a glucose solution" is limited to adding PEI, PEI-glu, PEI-gal, or PEI-man

to a solution of glucose + water or if the phrase encompasses PEI-glu, PEI-gal, or PEI-man + water. The specification teaches PEI may be glycosylated (pg 21, Table 1) or solubilized in glucose (pg 22, line 35). Overall, it is unclear whether the phrase is limited to PEI or PEI derivative added to glucose + water or if the phrase encompasses adding PEI-glu to water. Applicants' previous arguments relating to "unexpected results" were not persuasive because they did not address the indefiniteness of the phrase. Applicants argued both scenarios described by the examiner are encompassed by the phrase; however, PEI-glu added to water cannot be "a glucose solution" because the glucose will not solubilize in the water.

Applicants argue "it does not matter whether the glucose solution is a solution in which the complex of claim 23 is put in or encompasses a complex made up of PEI conjugated with glucose, because both have been shown to work, and are with the scope of the invention." Applicants' argument is not persuasive. Applicants' arguments state a solution comprising PEI conjugated with glucose is within the scope of the invention [as a whole] but do not address whether a solution comprising PEI conjugated with glucose is within the scope of the phrase "formulated in a glucose solution" in claim 30.

F. Claims 38 and 39 are newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Limiting the human immunodeficiency virus to replication-defective or integrase-defective HIV in claims 38 and 39 does not further limit

the protein from HIV in claim 37. Claims 38 and 39 should further limit the DNA of claim 23.

Claim Rejections - 35 USC § 102

IV. Claims 23-26, 28, 30-32, 35, 37, 40, 41 and 43 remain rejected under 35 U.S.C. 102(e) as being anticipated by Behr (US Patent 6,013,240, Jan. 11, 2000; 102(e) date=2-28-97) as supported by Carson (US Patent 5,679,647), Mittal (J. General Virol., Jan. 1996, Vol. 77, pg 1-9, abstract only) and Kuby (ed., Immunology, 1992, W.H. Freeman and Company, Chapter 1, "Acquired Immunity," pg 8-9) for reasons of record.

Parent application 60/058,933 did not describe complexing DNA with a compound selected from the group consisting of sugars, PEI or PEI derivatives (claim 23). Therefore, claim 23 does not get priority back to parent application 60/058,933 (filed 9-15-97). Parent application 09/153,198 (filed 9-15-98) described complexing DNA with PEI-mannose in a 5-10% glucose solution on pg 26, lines 1-9. Therefore, claim 23 has priority to 9-15-98.

Behr taught a complex comprising i) PEI, and ii) plasmid DNA comprising a nucleic acid sequence encoding luciferase operatively linked to a promoter suspended in 5% glucose (col. 12, lines 53-57). Behr taught administering any complex of the invention to the skin or mucosa of an animal (claim 33, col. 6, lines 1-19). More specifically, Behr taught topical, cutaneous, oral, rectal, vaginal, parenteral and intranasal application (col. 6, lines 1-4), which is equivalent to applying the gene delivery complex to the skin or mucosa as claimed.

The method of Behr inherently results in transfecting APCs because dendritic cells (a type of antigen presenting cell) are found in the epidermis (see definition of "dendritic cell", item 3). While not relied upon for the basis of the rejection, Carson provides evidence that a gene delivery complex applied to the skin intradermally transfects dendritic cells (col. 36-37, Examples 11-12). Intradermal application is equivalent to applying DNA to the skin because it puts the DNA in physical contact with the skin. It is noted, however, the phrase "transfecting antigen presenting cells" in the preamble does not bear patentable weight in considering the art because the body of the claim does not require transfecting APCs.

Luciferase is an immunogenic protein because it is foreign to mammals and induces an immune response in mammals. Mittal taught luciferase induces antibodies in rats (second to last sentence of the abstract). Luciferase must be immunogenic as claimed in any animal other than fireflies because it is a protein isolated from fireflies and because proteins isolated from one animal and introduced into another animal are recognized as foreign by the immune system and cause an immune response (Kuby, pg 8-9). In the alternative, Behr taught the DNA could encode an HIV peptide (col. 3, lines 57-67).

Claims 25, 26 and 43 are included because they are not limited to a compound that is mannosylated PEI or PEI "from a PEI 22 kDA;" claims 25, 26 and 43 encompass non-sugar-modified PEI solubilized in glucose as in parent claim 24.

Claims 28 and 30 are included because Behr taught that between 5-20 equivalents of PEI amines are used relative to one DNA phosphate (col. 8, lines 15-19).

The instant specification teaches that the ratio of 5:1 cause the complex to be electrostatically neutral (¶ bridging pg 21-22).

Claim 33 has been excluded because 5% is not "8%" as newly amended.

Claims 35 and 41 are included because administering the complex to the skin/mucosa as taught by Behr inherently would activate APCs by toxin activation. Cells would start expressing luciferase and this firefly "toxin" would be recognized as foreign by the animal, thereby activating APCs, including Langerhans cells.

The 102 rejection is made based on the breadth of the claim and does not conflict with the enablement rejection. The sole disclosed use of treatment or prophylaxis at issue in the enablement rejection is not given weight when considering the art.

Response to arguments

Applicants' argue no evidence exists that an immune response to luciferase occurs; therefore, applicants' conclude that the examiner's assertion that luciferase is an immunogenic protein is in error. Applicants request evidence that an immune response to luciferase occurs. Applicants argue luciferase is non-toxic; therefore, applicants conclude luciferase is not an immunogenic protein. Applicants' arguments are not persuasive. Behr also teaches using HIV antigens. Furthermore, scientific reasoning is adequate to support the examiner's assertion of inherency regarding luciferase. Luciferase is foreign to mammals; foreign proteins induce an immune response in mammals; therefore, luciferase is an immunogenic protein as claimed. Finally, Mittal taught luciferase induces antibodies in rats (second to last sentence of the

abstract). Just because luciferase is not toxic does not mean luciferase fails to be immunogenic.

Applicants argue Behr suggested avoiding immunogenicity. Applicants' argument is not persuasive under anticipation because Behr taught all the steps and reagents required to apply DNA encoding an immunogenic protein to the skin as claimed. Luciferase is an immunogenic protein because it is a foreign protein that would induce an immune response for reasons of record. HIV antigen is clearly an "immunogenic protein."

Applicants argue the experiments in the instant application used a different marker gene. Applicants' argument is irrelevant because Behr taught DNA encoding luciferase or HIV antigen and because the claims are not limited to DNA encoding GFP.

Applicants argue Behr does not disclose transfecting antigen presenting cells (APCs), targeting of APCs, or formulations that can be used for needleless delivery of genes in vivo. Applicants' arguments are not persuasive. The claims are not limited to needless injection. The method steps described by Behr are described in the instant application as being part of the invention and are encompassed by claim 23. In addition, Carson supports the fact that at least DNA applied to the skin intradermally transfects APCs. Finally, the limitation of "transfecting APCs" in the preamble is an intended use and does not bear patentable weight in considering art because it does not necessarily have to occur.

Applicants argue Carson does not provide evidence that a gene delivery complex applied to the skin would transfect dendritic cells. Applicants argue Carson is limited to

DNA only in saline. Applicants' argument is not persuasive. It is reasonable to conclude from Carson that DNA + carrier applied intradermally would transfect dendritic cells. The addition of PEI or glucose to DNA as taught by Behr would have transfection of APCs. Furthermore, transfecting APCs in the preamble of claim 23 is an intended use and does not bear patentable weight in considering art because it does not necessarily have to occur. Applicants argue the material tested by Carson did not work in the brain. Applicants' argument is moot because it worked when applied to the skin. Applicants' argue the CTL response observed by Carson indicates uptake by different classes of cells. Applicants' argument is unfounded. The CTL response observed by Carson indicates antigen presentation, i.e. APCs were transfected. Applicants' arguments on pg 33 regarding Carson are noted but are not persuasive because "applying a complex to the skin" as claimed encompasses intradermal injection as described by Carson.

Applicants argue Behr does not teach the PEI derivative targets the mannose receptor in claim 25. Applicants' argument is not persuasive. Claim 25 is not limited to a compound that is mannosylated PEI or PEI "from a PEI 22 kDA;" claim 25 encompasses non-sugar-modified PEI solubilized in glucose as in parent claim 24.

Applicants argue Behr does not teach the PEI derivative is mannosylated PEI as in claim 26. Applicants' argument is not persuasive. Claim 26 is included because it is not limited to a compound that is mannosylated PEI or PEI "from a PEI 22 kDA;" claim 26 encompasses non-sugar-modified PEI solubilized in glucose as in parent claim 24.

Applicants' arguments regarding Behr as they relate to the dependent claims (pg 32 of the Brief) are noted but have all been addressed in the basis of the rejection. Behr taught applying DNA complexed with PEI in a 5% glucose solution to the skin or mucosa topically, cutaneously, etc., which meets the limitations of the claims.

Applicants argue there is no evidence that the material disclosed by Behr in Experiment 14 would inherently transfect APCs. Applicants argue Behr does not provide a reasonable expectation of successfully transfecting APCs as claimed. Applicants' arguments are not persuasive. Applicants disclose applying plasmid DNA and PEI in a glucose solution to the skin intradermally (pg 25, line 6, "This is expected to significantly increase the efficacy of present vaccine strategies. For example, mixing vaccines with sugar for subcutaneous, intradermal and intramuscular injection of DNA and protein antigens") as being part of the claimed invention. The steps described by Behr encompass applying DNA encoding HIV by a number of means; there is no reason to doubt the complex described by Behr would inherently transfect APCs because the steps are identical to those described by applicants. In particular, Carson discloses intradermal delivery of DNA in saline as transfecting APCs; there is no reason to doubt the addition of PEI and glucose would inhibit transfection of APCs. Furthermore, transfecting APCs in the preamble of claim 23 is an intended use and does not bear patentable weight in considering art because it does not necessarily have to occur.

Applicants argue intracerebral injection of naked DNA encoding luciferase failed to work as discussed by Behr in Example 14 (column 13, lines 9-10; pg 28 of

arguments). Applicants' argument is not persuasive. The teachings of Behr are not limited to intracerebral injection of naked DNA.

Applicants argue Behr used GFP. Applicants' argument is not persuasive. The claims encompass DNA encodes GFP because it is a foreign protein that would induce an immune response. Furthermore, Behr disclosed replacing the marker protein with HIV. Applicants' arguments regarding the transgenic bunny born to express GFP are moot because the GFP is recognized as a "self" protein in the transgenic bunny; its immune system developed recognizing GFP as part of itself.

Applicants argue Carson does not provide a reasonable expectation of successfully transfecting APCs because Carson used intradermal injection or a tine devise. Applicants' arguments are not persuasive. The claims encompass intradermal injection or a tine devise. The claims are not limited to applying the gene delivery complex to the skin topically.

Claim Rejections - 35 USC § 103

V. Claims 23-26, 28, 30-32, 35, 37-41 and 43 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Behr (US Patent 6,013,240, Jan. 11, 2000) as supported by Carson (US Patent 5,679,647), Mittal (J. General Virol., Jan. 1996, Vol. 77, pg 1-9, abstract only) and Kuby (ed., Immunology, 1992, W.H. Freeman and Company, Chapter 1, "Acquired Immunity," pg 8-9) and in view of Holler (US Patent 5,908,923) for reasons of record.

Parent application 60/058,933 (9-15-97) did not describe complexing DNA with a compound selected from the group consisting of sugars, PEI or PEI derivatives (claim

23). Parent application 09/153,198 (9-15-98) described complexing DNA with PEI-mannose in a 5-10% glucose solution on pg 26, lines 1-9; therefore, claim 23 has priority to 09/153,198 (9-15-98).

Behr taught a complex comprising i) PEI, and ii) plasmid DNA comprising a nucleic acid sequence encoding luciferase operatively linked to a promoter suspended in 5% glucose (col. 12, lines 53-57). Luciferase is an immunogenic protein because it is foreign to mammals and induces an immune response in mammals. Behr taught administering the complex to the skin or mucosa of an animal (claim 33, col. 6, lines 1-19). Behr taught the DNA could encode a peptide from HIV (col. 3, lines 57-67). The method of Behr inherently results in transfecting APCs because dendritic cells. Carson provides evidence for the examiner's assertion of inherency by teaching a gene delivery complex applied to the skin transfects dendritic cells (col. 36-37, Examples 11-12). Case law established that reliance upon inherency in an obviousness rejection (103) instead of an anticipation rejection (102) is proper. In re Skoner, et al. 186 USPQ 80 (CCPA). It is noted, however, that the phrase "transfecting antigen presenting cells" in the preamble does not bear patentable weight in considering the art because it may not occur.

Claims 25, 26 and 43 are included because they are not limited to a compound that is mannosylated PEI or PEI "from a PEI 22 kDA;" claims 25, 26 and 43 encompass non-sugar-modified PEI solubilized in glucose as in parent claim 24.

Claims 28 and 30 are included because Behr taught that between 5-20 equivalents of PEI amines are used relative to one DNA phosphate (col. 8, lines 15-19).

The instant specification teaches that the ratio of 5:1 cause the complex to be electrostatically neutral (¶ bridging pg 21-22).

Claim 33 has been excluded because 5% is not "8%" as newly amended.

Claims 35 and 41 are included because administering the complex to the skin/mucosa as taught by Behr inherently would activate APCs by toxin activation. Cells would start expressing luciferase and this firefly "toxin" would be recognized as foreign by the animal, thereby activating APCs, including Langerhans cells.

Behr did not teach using a plasmid encoding a protein from a replication-defective, integrase-defective HIV.

However, Holler taught a plasmid encoding a replication-defective HIV that was integrase defective for use in vivo (col. 4, lines 51-54).

Thus, it would have been obvious for one of ordinary skill in the art at the time the invention was made to apply a gene delivery complex comprising a plasmid encoding an HIV protein to the skin/mucosa of an animal as described by Behr, wherein the plasmid encoded a replication-defective, integrase-defective HIV as taught by Holler. One of ordinary skill in the art would have been motivated to make the HIV replication-defective and integrase-defective to prevent causing disease in the animal.

The combined teachings of Behr and Holler provide a reasonable expectation of successfully transfecting cells because Holler transfected CEM (a lymphoblastoid cell line) with integrase-defective HIV. Therefore, one of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of successfully

transfecting APCs by applying the plasmid encoding the HIV taught by Holler to the skin or mucosa as taught by Behr.

The examiner acknowledges that interpreting the claims as not requiring treating or preventing HIV under 103 is different than interpreting the claims as requiring treating or preventing HIV under written description and enablement; however, both interpretations are reasonable and all rejections have been fully supported. Assuming arguendo that the limitation of treating or preventing HIV cannot be read into the claim, the burden required to show motivation to combine Behr and Holler under obviousness is not high because the claims merely require applying a vector encoding HIV to the skin or mucosa of an animal, because Holler (and numerous other references) taught a vector encoding HIV proteins for use in vivo and because Behr suggested using a vector encoding HIV proteins in his method of transfecting in vivo. The rejection of claims 37-39 under 103 is made because of the breadth of the claims (merely transfecting antigen presenting cells) and does not conflict with the enablement rejection which is based on the sole disclosed use for transfecting antigen presenting cells (for treatment or prophylaxis). Treatment and prophylaxis are not given weight when considering the art.

Response to arguments

Applicants argue Behr teaches avoiding immunogenicity. Applicants' argument is not persuasive. While Behr taught avoiding immunogenicity in one section, the teachings of Behr are not limited to avoiding immunogenicity because Behr used GFP,

a foreign protein to mammals, and suggests replacing it with HIV antigens (col. 3, lines 57-67).

Applicants argue the instant invention is not gene therapy like the method of Behr. Applicants' argument is not persuasive because the claims require applying DNA to the skin or mucosa of an animal to transfect APCs.

Applicants argue Behr suggests using PEI in a variety of cells in a wide range of ratios without any distinction as to what might be accomplished by varying the ratios or varying the targeting elements. Applicants argue Behr suggests various routes of delivery (col. 6, lines 1-4) without any distinction of an advantage that might be obtained. Applicants acknowledge Behr prefers direct injection and topical administration but argue only direct injection into the brain is disclosed in an experiment. Applicants' arguments are not persuasive. Behr need not disclose benefits of various "targeting elements" or their ratios to meet the limitations claimed. Behr need not exemplify topical administration to meet the limitation of "applying DNA to the skin or mucosa." Behr provides a reasonable expectation of successfully applying DNA encoding an antigen complexed with PEI in a 5% glucose solution to the skin or mucosa, which inherently transfects APCs as claimed.

Applicants argue Behr does not teach how to realize the full potential of the invention claimed. Applicants' argument is not persuasive. Behr requires no such teaching; Behr provides all the steps and reagents required to transfect APCs.

Applicants again argue Behr cannot be relied upon for applying a plasmid encoding an HIV antigen to the skin because the reference shows no such thing.

Applicants' argument is not persuasive. No such example is required by Behr; Behr provides all the steps and reagents required to transfect APCs with a plasmid encoding an HIV antigen as claimed.

Applicants assert numerous claim limitations are missing from the Behr reference. Applicants' arguments are not persuasive and are addressed throughout the basis of the rejection and the response to arguments.

Applicants argue Carson does not provide a reasonable expectation of successfully transfecting APCs because Carson used intradermal injection or a tine devise. Applicants' arguments are not persuasive. The claims encompass applying the gene delivery complex to the skin using an intradermal injection or a tine devise. None of the claims are limited to topical application. The teachings of Carson relate to applying the gene delivery complex to the skin using an intradermal injection or a tine devise, which is encompassed by the claims.

Applicants acknowledge the Holler reference suggests the plasmid encoding a replication-defective HIV that was integrase defective for use in vivo (col. 4, lines 51-54) but argue Holler does not teach the method steps claimed. Applicants' argument is not persuasive. Holler need not teach the method steps to apply a plasmid in vivo to be used in an obviousness rejection. Behr provides the method steps needed to apply the plasmid of Holler to the skin or mucosa of an animal as claimed. One of ordinary skill would have recognized from the suggestion by Holler to use the HIV vector in vivo that the method of Behr would apply because Behr suggested using his method to introduce DNA encoding HIV proteins.

Applicants' arguments regarding transfection "efficiency" are noted but are misplaced; any amount of transfection "efficiency" is adequate to meet the claims. There is no reason to believe any of the methods of delivery to the skin or mucosa of a mammal described by Behr would fail to transfect APCs.

Applicants mention clinical trials (pg 42, "A vaccine according...") but do not correlate the clinical trial to the teachings in the specification or the claims. Applicants argue the clinical trials are evidence of non-obviousness. Applicants argue a declaration was filed to this effect. Applicants' arguments are not persuasive. The clinical trials are inadequate to show unexpected results over the combined teachings of Behr (supported by Carson) and Holler because the clinical trials are limited to DNA encoding a specific retroviral vector with PEI-man and glucose applied transcutaneously which is broader than any claim pending and because the clinical trials require combining the application of the gene delivery treatment with HAART (antiviral drug therapy), which was not disclosed in the instant application. The declaration filed 1-5-07 also fails to overcome any of the references by swearing behind them. Accordingly, the Declaration and clinical trials fail to overcome the obviousness rejection.

Applicants argue the compounds used for delivery must "target" APCs. Applicants' argument is not persuasive. The claims encompass using PEI or glucose as taught by Behr. Without evidence to the contrary, PEI and glucose "target" APCs as claimed because PEI and sugars are disclosed by applicants as being part of the invention. If applicants intend claim 23 to be limited to only certain PEI, PEI-derivatives or sugars that "target" APCs, the species within that genus cannot be determined. In

particular, if PEI is inadequate to "target" APCs, it is unclear why it is specifically set forth as one of the species of compounds in claim 23. Applicants are reminded that because of the open language in claim 24 (glucose is also included), claim 25 (it limits the PEI-derivatives of claim 24 but still encompasses glucose), and claim 26 (it limits the PEI-derivative of claim 25 but still encompasses glucose), claims 24-26 do not limit the "one or more compounds" to PEI derivatives.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

VI. Claims 23-26, 28, 30-33, 35 and 37-43 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 58-72 of copending Application No. 08/803484 in view of the disclosure of '484. Although the conflicting claims are not identical, they are not patentably distinct from

each other. Claim 58 is drawn to a method for raising a cellular immune response in a mammal, the steps comprising transducing antigen presenting cells selected from the group consisting of Langerhans cells and dendritic cells with a plasmid DNA construct that encodes a replication-defective retrovirus, and exposing a mammal to the cells in a manner that allows the cells to express the construct in the lymphoid organs of the mammal, whereby a cellular immune response to the retrovirus is raised by the mammal. Claim 58 could simply be drawn to a method of transfecting antigen presenting cells as now claimed in the instant application. The limitation of applying the gene delivery complex to the skin in claim 23 of the instant application encompasses intradermal administration, which is taught on pg 32, Example 14, (a). The genus of animal now claimed is obvious in view of pg 4, line 19, of '484. The limitation of one or more sugar, PEI or PEI derivative in claim 23 encompasses PEI delivery as on pg 38, line 20. The integrase-defective replication-defective retroviral vector in claims 38 and 39 of this application is obvious in view of claim 64 and Example 2 on pg 18 of '484. Two-way obviousness exists in this case because the teachings of '484 are incorporated by reference on pg 4, lines 29-32, of the instant application. The claims now in '484 can be claimed in the instant application. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached at the office on Monday, Tuesday, Thursday and Friday from 9:30 am to 6:00 pm at 571-272-0738.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Peter Paras, can be reached on 571-272-4517.

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